Inhibition of the Effect of Reserpine on Motor Control by Drugs which Influence Reserpine Rigidity

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vorgelegt von

Gerd Lanzer

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Inhibition of the Effect of Reserpine on Motor Control by Drugs which Influence Reserpine Rigidity*

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Summary. The effect of monoaminergic (DOPA, metamphetamine, propylhexedrine) and cholinolytic agents (atropine, biperiden, caramiphen, trihexyphenidyl) on α and γ reflex discharge from the spinal cord was studied in the rat. For comparison, the anticonvulsant phenytoin was included in the investigation. All drugs antagonized the action of a high dose of reserpine on motor control by reducing the increased α and increasing the diminished γ reflex activity. The latency of α reflex discharge shortened by reserpine was increased by the drugs. The results provide further support of the view that disturbance of motor control caused by reserpine in the rat derives from an imbalance between monoaminergic and cholinergic systems in the brain.

Key-Words: Spinal motor activity — Reserpine — Monoaminergic agents — Cholinolytic agents — Antiparkinson drugs — Phenytoin.

Schlüsselwörter: spinalmotorische Aktivität — Reserpin — Monoaminergica — Cholinolytica — Antiparkinsonstoffe — Phenytoin.

Reserpine rigidity in the rat has been shown by Steg and coworkers to develop on the background of increased α and decreased γ motor activity (Steg, 1964; Arvidsson *et al.*, 1966). Since atropine as well as L-DOPA depress rigidity and "normalize" spinal motor control, it has been proposed that reserpine rigidity is due to a disturbed balance between monoaminerigc and cholinergic mechanisms in the brain, and that drugs which either stimulate monoaminergic or depress cholinergic functions restore normal motor activity. Accordingly, also sympathomimetic amines such as metamphetamine and its hydrogenated derivative propylhexedrine, and the cholinolytic agent biperiden were able to abolish reserpine rigidity (Jurna, 1968b). It remained to verify whether these drugs decrease α and increase γ motor activity after an application of reserpine.

Experiments were therefore carried out in which the effect of metamphetamine, propylhexedrine and biperiden on motor activity disturbed by reserpine was assessed. Part of the results have already been presented (Jurna, 1968a). For comparison, also experiments with

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atropine and L-DOPA were made, in which similar results were obtained as by STEG and coworkers (ROOS and STEG, 1964; ARVIDSSON *et al.*, 1966). To supplement the number of antiparkinson drugs with cholinolytic properties, caramiphen and trihexyphenidyl were included in this study. Finally, the anticonvulsant agent phenytoin was tested because of its effectiveness against reserpine rigidity (JURNA, 1968b).

Methods

The experiments were performed on 173 Wistar rats of 250—350 g body weight operated in halothane anesthesia. After the operation, anesthesia was kept at a level which allowed rigidity to develop. Preparation of the animals and recording of α and γ motor activity was made according to the procedure described by STEG (STEG, 1964; ROOS and STEG, 1964; ARVIDSSON *et al.*, 1966). After laminectomy, the animals were fixed rigidly. A thin filament was isolated from a ventral root supplying the calf muscles of the left hind leg. Activity of α and γ motor axons was led off with two pairs of electrodes about 5 mm apart and displayed on a dual beam oscilloscope. Reflex activity was elicited by electrical stimulation of the corresponding dorsal root with single impulses. Apart from differences in shape and amplitude, the different conduction velocities served to distinguish α and γ units. Electromyographical activity was recorded from the calf muscles at rest and during stretch elicited by dorsiflexion of the foot.

During the control period, 15 and 30 min after the injection of reserpine, and 10, 30 and 40 min after the injection of the drugs tested, about 20 recordings were made each time. The number of α and γ reflex discharges per sweep (sweep speed 1 msec/cm) was counted and pooled for calculation. The tables presented in the part dealing with the results show the differences in α and γ activity caused by reserpine and/or the drugs; in each experiment the values of either α or γ discharges of the control period were substracted from the α or γ values obtained after reserpine, and the α or γ values obtained after reserpine were subtracted from the corresponding values after application of one of the subtances tested; from these differences the mean values were determined, which are expressed as differences in α or γ discharge. Moreover, the ratio of α and γ discharges was determined and is presented under the heading "α/γ quotient" (ARVIDSSON *et al.*, 1966).

All substances were administered by a cannula inserted into one of the tail veins. The drugs used were reserpine (Sedaraupin®, C. F. Boehringer & Soehne, Mannheim) in a dose of 10 mg/kg, DOPA (L-dihydroxyphenylalanine) dissolved 1% in saline by heating up to 75° C under constant stirring, metamphetamine (D-metamphetamine hydrochloride), propylhexedrine (N-methyl-β-cyclohexylisopropylamine, Eventin®, Knoll, Ludwigshafen), atropine (atropine sulfate), biperiden (1-[bicyclo-(2.2.1)hept-2-en-5-yl]-1-phenyl-3-piperidinopropan-1-ol, Akineton®, Knoll, Ludwigshafen), caramiphen(1-phenylcyclopentanecarboxylic acid 2-diethylaminoethyl ester, Parpanit®, Geigy, Basel), trihexyphenidyl (1-cyclohexyl-1-phenyl-3-piperidino propan-1-ol, Artane®, Lederle, München), and phenytoin (diphenylhydantoin-Na).

Results

I. Effect of Reserpine on α and γ Motor Discharge

Reserpine injected intravenously in a dose of 10 mg/kg caused an increase of α and a decrease of γ reflex activity, as has already been reported by STEG (1964) and confirmed repeatedly since (ROOS and

STEG, 1964; ARVIDSSON *et al.*, 1966). The effect of the alkaloid was maximally developed 30 min after the application and stayed unchanged for hours. The values obtained at 30 min after reserpine were chosen to make calculations and to determine drug effects.

The number of α reflex discharges per sweep (sweep speed 1 msec/cm) in the control period amounted to 2.8 ± 2.0 (mean $\pm$ standard deviation), and of the γ reflex discharges to 6.6 ± 2.8. After reserpine, the mean of α reflex discharges was 6.2 ± 2.9, and of γ reflex discharges 4.6 ± 2.3. The number of experiments was 102. The increase in α and decrease in γ reflex activity caused by reserpine was statistically significant ($p < 0.001$) All experiments in which the alkaloid had been applied were used for the evaluation.

Furthermore, it was observed that α reflex discharge started earlier in the presence of reserpine. When the interval between the stimulus artifact and the first α discharge in all recordings made during the control period was measured and plotted against the frequency expressed in per cent of the total number of determinations, a distribution was obtained, which showed two maxima, one at about 2.0 msec, and the other at about 3.0 msec (Fig. 1 A, faint lined—shaded area). The distribution of the reserpine values has only one maximum, which appears earlier than the first maximum of the controls, i.e. at about 1.5 msec (Fig. 1 A, heavy lined area).

II. Effect of DOPA, Methyamphetamine and Propylhexedrine

DOPA given in a dose of 100 mg/kg after reserpine abolished rigidity and tended to "normalize" α and γ motor activity, which is in accordance with the findings of STEG and coworkers (ROOS and STEG, 1964; ARVIDSSON *et al.*, 1966). An example of an experiment with reserpine and DOPA is presented in Fig. 2. During the control period, there was only phasic activity in the electromyogram. Recording from the ventral root filament showed little α, but rather high γ reflex activity. Reserpine caused tonic activity to appear during stretch of the calf muscles, that is, rigidity had developed. Concomitantly, α reflex activity had increased, α activity was present also spontaneously, the interval between stimulus artifact and the first α discharge was shortened, and γ reflex activity was reduced. DOPA was given immediately after the recordings 30 min after the injection of reserpine had been made. It abolished rigidity and brought α and γ reflex activity back to the control level. The mean values of α an γ reflex discharges counted per sweep in the recordings of the control period, after reserpine and after DOPA are presented in the diagram.

The results obtained in eight experiments with reserpine and DOPA are summarized in Table 1. Reserpine increased α and decreased γ reflex activity as indicated by the differences in discharge. Comparison of the

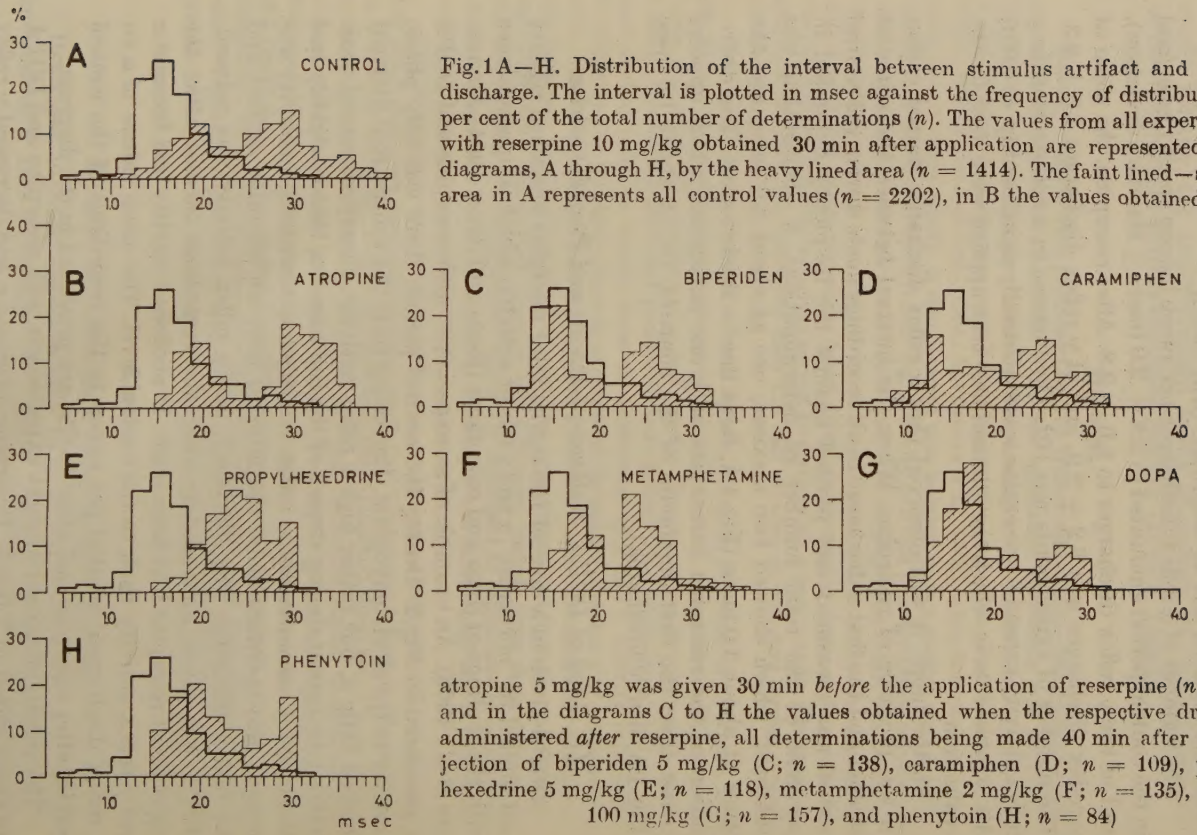

Fig. 1 A—H. Distribution of the interval between stimulus artifact and first α discharge. The interval is plotted in msec against the frequency of distribution in per cent of the total number of determinations (n). The values from all experiments with reserpine 10 mg/kg obtained 30 min after application are represented in all diagrams, A through H, by the heavy lined area ($n = 1414$). The faint lined—shaded area in A represents all control values ($n = 2202$), in B the values obtained when atropine 5 mg/kg was given 30 min *before* the application of reserpine ($n = 96$), and in the diagrams C to H the values obtained when the respective drug was administered *after* reserpine, all determinations being made 40 min after the injection of biperiden 5 mg/kg (C; $n = 138$), caramiphen (D; $n = 109$), propylhexedrine 5 mg/kg (E; $n = 118$), metamphetamine 2 mg/kg (F; $n = 135$), DOPA 100 mg/kg (G; $n = 157$), and phenytoin (H; $n = 84$)

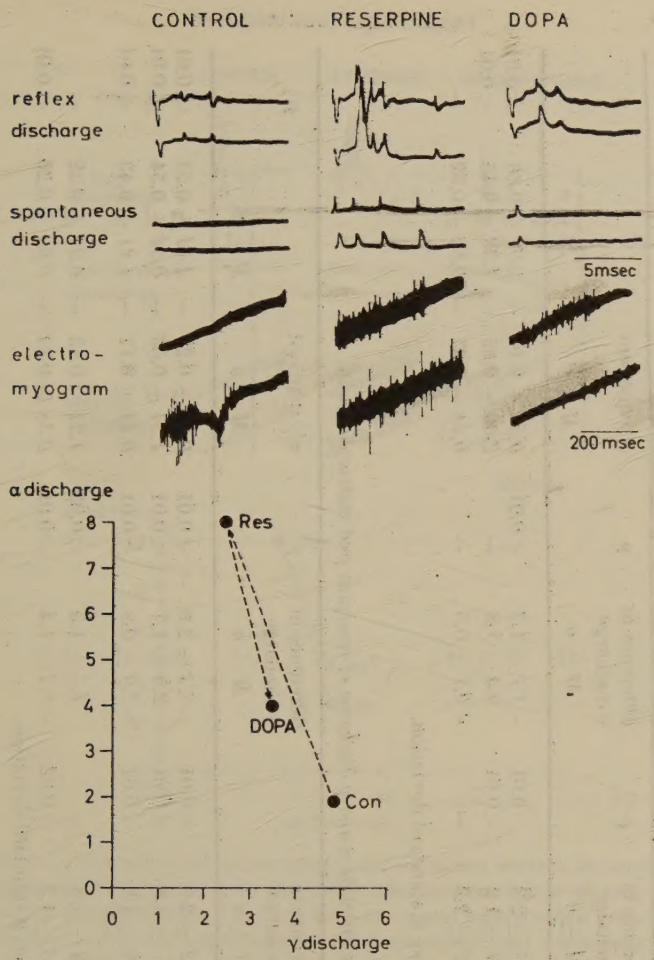

Fig. 2. Effect of reserpine and DOPA on motor control. Upper row of records: reflex discharge led off from ventral root filament following stimulation of corresponding dorsal root with single impulse. Middle row of records: spontaneous discharge from ventral root filament. Upper tracing: recording made with electrode proximal to the spinal cord; lower tracing: recording made with distal electrode. Recordings with running beam on stationary film. Lower row of recordings: electromyographical activity led off from the calf muscles. Recording made with running beam on moving film. First column of records: control recordings showing little α but high γ reflex discharge and phasic activity in the electromyogram during quick stretch of the muscles. Second column of records: recordings made after the injection of reserpine 10 mg/kg, showing high α and little γ activity, shortening of the interval between stimulus artifact and first α discharge, spontaneous α activity, and tonic activity in the electromyogram during sustained stretch of the muscles. Third column of records: recordings made 40 min after the injection of DOPA 100 mg/kg, showing depression of α and electromyographical activity. The diagram represents the mean values of the number of α and γ reflex discharge per sweep during the control period *Con*, after reserpine *Res*, and after *DOPA*

Table 1. *The effect on α and γ discharge of reserpine and DOPA*

n	substances (mg/kg)	difference in α discharge $M \pm \sigma$	p	difference in γ discharge $M \pm \sigma$	p	α/γ quotient $M \pm \sigma$	—	$M \pm \sigma$	p
8	control — reserpine 10	*4.5* ± 2.3	<0.01	*−1.7* ± 1.2	<0.01	*0.55* ± 0.10	—	*2.09* ± 0.66	<0.01
	reserpine 10 — DOPA 100	*−1.2* ± 1.2	<0.01	*0.5* ± 1.8	—	*2.09* ± 0.66	—	*1.38* ± 0.45	<0.01
6	control — DOPA 100	*2.2* ± 2.3	—	*−0.7* ± 0.5	—	*0.48* ± 0.37	—	*0.82* ± 0.32	—

n number of experiments; M mean value; σ standard deviation.

Table 2. *The effect on α and γ discharge of reserpine and metamphetamine*

n	substances (mg/kg)	difference in α discharge $M \pm \sigma$	p	difference in γ discharge $M \pm \sigma$	p	α/γ quotient $M \pm \sigma$	—	$M \pm \sigma$	p
7	control — reserpine 10	*4.2* ± 2.0	<0.01	*−3.4* ± 2.8	<0.01	*0.46* ± 0.23	—	*1.44* ± 0.53	<0.01
	reserpine 10 — metamphetamine 2	*−3.7* ± 1.8	<0.01	*2.9* ± 1.7	<0.01	*1.44* ± 0.53	—	*0.54* ± 0.54	<0.01
7	control — reserpine 10	*3.9* ± 1.9	<0.01	*−2.0* ± 0.8	<0.01	*0.44* ± 0.17	—	*1.21* ± 0.43	<0.01
	reserpine 10 — metamphetamine 0.1	*−0.4* ± 1.8	—	*1.3* ± 1.3	<0.05	*1.21* ± 0.43	—	*0.91* ± 0.42	—
8	control — metamphetamine 2	*1.3* ± 1.3	<0.02	*−2.3* ± 1.4	<0.01	*0.38* ± 0.14	—	*0.69* ± 0.26	<0.01

n number of experiments; M mean value; σ standard deviation.

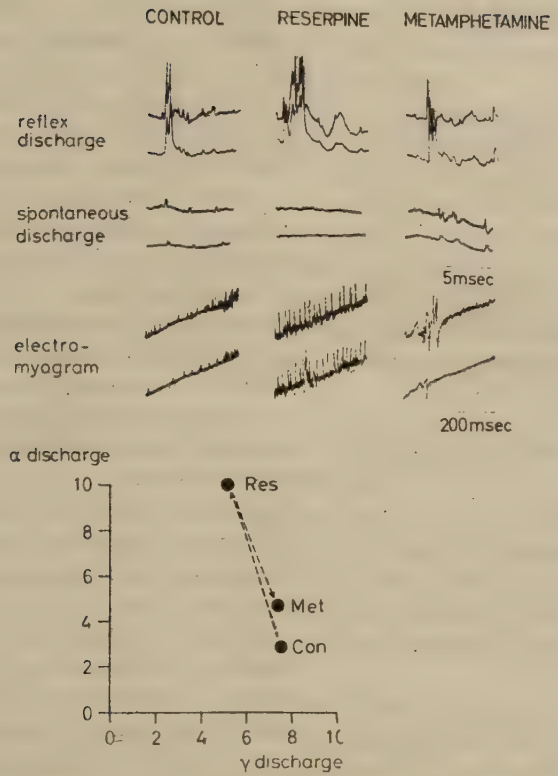

Fig. 3. Effects of reserpine and metamphetamine on motor control. Recordings as in Fig. 2. The records represented in the third column were taken 40 min after the injection of metamphetamine 2 mg/kg. Note low α and high γ reflex activity in the control, high α and low γ reflex activity after reserpine, and depression of α and increase in γ reflex discharge after metamphetamine. The diagram summarizes the experiment, giving the mean values of the number of α and γ reflex discharges per sweep during the control period *Con*, after reserpine *Res*, and after metamphetamine *Met*

ratios of α and γ discharges yields a significant increase of the α/γ quotient after reserpine. According to ARVIDSSON *et al.* (1966), the α/γ quotient may serve as an index for the state of balance between α and γ motor systems, where a quotient of > 1 means predominance of α activity, and a quotient of < 1 predominance of γ activity. DOPA diminished α and increased γ reflex activity, though not very markedly. Nevertheless, the α/γ quotient is significantly lowered. However, the distribution of the frequency of the interval between stimulus artifact and the first α-reflex discharge does not show a distinct change (Fig. 1 A). The effects of DOPA was maximal about 30 to 40 min after the injection, and the

Table 3. *The effect on α and γ discharge of reserpine and propylhexedrine*

n	substances (mg/kg)	difference in α discharge $M \pm \sigma$	*p*	difference in γ discharge $M \pm \sigma$	*p*	α/γ quotient $M \pm \sigma$	$M \pm \sigma$	*p*
7	control — reserpine 10	6.2 ± 2.3	< 0.01	−3.0 ± 2.3	< 0.01	0.53 ± 0.28	1.88 ± 0.84	< 0.01
	reserpine 10 — propylhexedrine 5	−3.7 ± 3.0	< 0.01	3.4 ± 3.2	< 0.01	1.88 ± 0.84	0.73 ± 0.15	< 0.01
8	control — reserpine 10	2.2 ± 1.6	< 0.01	−0.5 ± 0.8	< 0.05	0.40 ± 0.43	1.00 ± 0.28	< 0.01
	reserpine 10 — propylhexedrine 2	−0.6 ± 0.7	< 0.05	2.9 ± 1.7	< 0.01	1.00 ± 0.28	0.52 ± 0.14	< 0.01
8	control — propylhexedrine 5	1.9 ± 1.9	< 0.01	1.5 ± 1.1	< 0.01	0.34 ± 0.14	0.98 ± 0.30	—
8	control — propylhexedrine 2	1.6 ± 1.5	—	1.7 ± 2.0	—	0.32 ± 0.33	0.56 ± 0.22	—

n number of experiments; *M* mean value; σ standard deviation.

values obtained at 40 min were chosen for making calculations. When DOPA was given alone, i.e. without previous administration of reserpine, α and γ motor activity remained unchanged (Table 1).

Metamphetamine and its hydrogenated homologue propylhexedrine, which had proved to depress reserpine rigidity (JURNA, 1968b), were likewise able to antagonize the action of reserpine on α and γ motor activity. *Metamphetamine* was applied in a dose of 2 mg/kg and 0.1 mg/kg, but only with the higher dose a marked effect was obtained (Fig. 3; Table 2). In contrast to the other drugs tested, the effect of metamphetamine set in very rapidly, and was maximal already at 10 min after the injection. However, the values obtained at 40 min after the application of the amine were chosen for calculation. Besides restoring α and γ reflex activity, metamphetamine produced rhythmic bursts of motor activity in the electromyogram and spontaneous α discharges, as may be seen in Fig. 3.

The antagonism against reserpine applies also for the change in the interval between stimulus artifact and the first α discharge (Fig. 1F). After metamphetamine, the frequency of distribution shows a second maximum at about 2,5 msec, and the first maximum is shifted towards a longer interval.

When metamphetamine was given alone, it changed α and γ activity in a similar way as does reserpine: α reflex discharge was increased and γ reflex discharge decreased (Table 2).

However, the latency of the first α discharge was not shortened. It is interesting to notice that, although the α/γ quotient attains a value of > 1, no rigidity develops after metamphetamine.

Propylhexedrine applied in a dose of 5 mg/kg and 2 mg/kg inhibited the action of reserpine on motor control, the effect being maximal about 30 to 40 min after the injection. The results are summarized in Table 3. Moreover, it decreased the latency of α discharge, the frequency of distribution showing one maximum between 2.0 and 2.5 msec (Fig. 1 E). When given without pretreatment with reserpine, propylhexedrine in the higher dose (5 mg/kg) increased α as well as γ reflex activity, whereas in the lower dose (2 mg/kg) motor control remained unchanged. Rhythmic bursts of motor activity occurred particularly when the high dose was applied.

III. The Effect of Atropine, Biperiden, Caramiphen and Trihexyphenidyl

Two series of experiments were performed to test the effectiveness of *atropine* 5 mg/kg on motor control disturbed by reserpine. In one series, atropine was given immediately *after* the action of reserpine had been recorded, i. e. the sequence was the same as for the other substances. In the other series, atropine was injected 30 min *before* the administration of reserpine.

Arvidsson *et al.* (1966) succeeded to inhibit the action of reserpine on motor activity by pretreatment with atropine, but found it difficult to demonstrate an antagonizing effect when the drug was applied after the disturbance of motor control had fully developed. Similarly, it turned out to be much more effective to give atropine before than after reserpine, although in some experiments an injection of atropine made after the application of reserpine definitely abolished reserpine rigidity and brought α and γ motor activity towards the control level (Fig. 4). Statistical evaluation of the results of the two series of experiments shows clearly that applying atropine after reserpine diminishes α and increases γ reflex discharge only to a small extent, whereas pretreatment with atropine completely blocks the action of reserpine (Table 4). In keeping with this finding is the observation that the distribution of the interval between stimulus artifact and the first α discharge obtained when atropine was injected after reserpine was identical with the one of reserpine. However, the area plotted from the values of the experiments in which reserpine was injected after pretreatment with atropine is essentially the same as that of the controls, having a maximum at 2.0 msec and another at 3.0 msec (Fig. 1 B).

Biperiden in a dose of 5 mg/kg and 2 mg/kg depressed reserpine rigidity and normalized the disturbed motor activity (Table 5). The

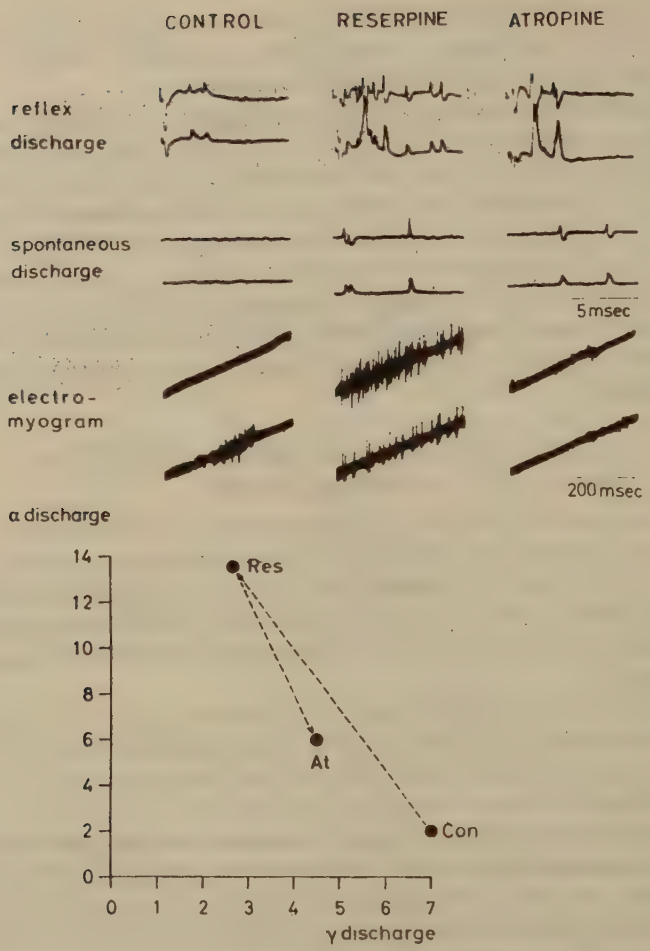

Fig. 4. Effect of reserpine and atropine on motor control. Recordings as in Fig. 2. The records of the third column were taken 40 min after the injection of atropine 5 mg/kg. The diagram summarizes the experiment, giving the mean values of the number of α and γ discharges per sweep during the control period *Con*, after reserpine *Res*, and after atropine *At*

effect of biperiden was maximal at about 40 min after the injection. An experiment carried out with biperiden 5 mg/kg given immediately after the recordings at 30 min after reserpine were made is illustrated by Fig. 5. Fig. 1C shows that the distribution of the interval between stimulus artifact and the first α reflex discharge after reserpine is changed by biperiden in such a way that a second maximum is built up at about 2.5 msec. When applied without reserpine pretreatment, biperiden slightly increased α reflex activity (Table 5).

Table 4. *The effect on α and γ discharge of reserpine and atropine*

n	substances (mg/kg)	difference in α discharge $M \pm \sigma$	*p*	difference in γ discharge $M \pm \sigma$	*p*	α/γ quotient $M \pm \sigma$	$M \pm \sigma$	*p*
8	control — reserpine 10	*5.8* ± 2.3	<0.01	*−3.8* ± 2.2	<0.01	*0.58* ± 0.46	*5.63* ± 3.98	<0.01
	reserpine 10 — atropine 5	*−1.5* ± 1.0	0.01	*1.4* ± 1.7	<0.05	*5.63* ± 3.98	*2.81* ± 2.30	—
6	control — atropine 5	*0.6* ± 1.6	—	*0.3* ± 1.1	—	*0.29* ± 0.10	*0.63* ± 0.60	—
	atropine 5 — reserpine 10	*0.2* ± 0.8	—	*−1.1* ± 0.7	—	*0.63* ± 0.60	*0.78* ± 0.75	—

n number of experiments; *M* mean value; σ standard deviation.

Table 5. *The effect on α and γ discharge of reserpine and biperiden*

n	substances (mg/kg)	difference in in α discharge $M \pm \sigma$	*p*	difference in γ discharge $M \pm \sigma$	*p*	α/γ quotient $M \pm \sigma$	$M \pm \sigma$	*p*
11	control — reserpine 10	*4.5* ± 2.5	<0.01	*−2.8* ± 1.8	<0.01	*0.37* ± 0.17	*2.18* ± 1.77	<0.01
	reserpine 10 — biperiden 5	*−1.8* ± 1.2	<0.01	*2.5* ± 1.5	<0.01	*2.18* ± 1.77	*0.95* ± 0.70	<0.01
7	control — reserpine 10	*2.3* ± 0.8	<0.01	*−1.4* ± 1.8	<0.05	*0.48* ± 0.23	*1.12* ± 0.38	<0.01
	reserpine 10 — biperiden 2	*−1.9* ± 1.6	<0.02	*1.0* ± 1.1	<0.05	*1.12* ± 0.38	*0.70* ± 0.43	<0.05
6	control — biperiden 5	*1.9* ± 3.1	—	*0.9* ± 2.7	—	*0.30* ± 0.14	*0.51* ± 0.20	<0.05

n number of experiments; *M* mean value; σ standard deviation.

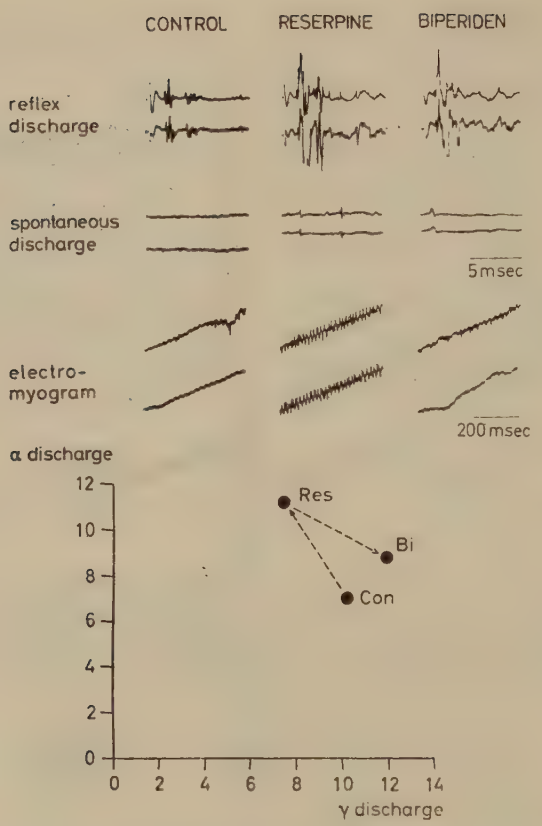

Fig. 5. Effect of reserpine and biperiden on motor control. Recordings as in Fig. 2. The records of the third column were taken after the injection of biperiden 5 mg/kg. The diagram summarizes the experiment, giving the mean values of the number of α and γ reflex discharges per sweep during the control period *Con*, after reserpine *Res*, and after biperiden *Bip*

Caramiphen and *trihexyphenidyl* given in a dose of 5 mg/kg depressed reserpine rigidity recorded electromyographically, antagonized the action of the alkaloid on motor control (Table 6), and shifted the frequency of distribution of the latency towards longer intervals (Fig. 1D).

IV. The Effect of Phenytoin

The effect of the anticonvulsant phenytoin on disturbed motor control was assessed because the drug antagonizes the action of reserpine not only in electroseizure but also in electromyographically recorded rigidity (JURNA, 1968b). Phenytoin in a dose of 50 mg/kg consistently "normalized" α and γ reflex activity (Fig. 6; Table 7). The effect was

Table 6. *The effect on α and γ discharge of reserpine, caramiphen and trihexyphenidyl*

n	substances (mg/kg)	difference in α discharge $M \pm \sigma$	*p*	difference in γ discharge $M \pm \sigma$	*p*	α/γ quotient $M \pm \sigma$	—	$M \pm \sigma$	*p*
9	control — reserpine 10	*3.8* ± 1.9	<0.01	*—1.4* ± 1.2	0.01	*0.56* ± 0.44	—	*2.03* ± 0.73	< 0.01
	reserpine 10 — caramiphen 5	*—2.7* ± 1.8	<0.01	*0.6* ± 1.4	—	*2.03* ± 0.73	—	*0.99* ± 0.75	< 0.01
7	control — caramiphen 5	*1.0* ± 1.4	—	*—0.3* ± 1.3	—	*0.27* ± 0.11	—	*0.43* ± 0.29	—
9	control — reserpine 10	*2.4* ± 1.7	<0.01	*—1.3* ± 1.6	<0.05	*0.62* ± 0.28	—	*1.73* ± 1.23	<0.01
	reserpine 50 — trihexyphenidyl 5	*—2.3* ± 1.9	<0.01	*0.4* ± 0.8	—	*1.73* ± 1.23	—	*0.78* ± 1.01	< 0.05
9	control — trihexyphenidyl 5	*1.3* ± 1.6	<0.05	*0.1* ± 1.4	—	*0.43* ± 0.21	—	*0.68* ± 0.18	—

n number of experiments; *M* mean value; σ standard deviation.

Table 7. *The effect on α and γ discharge of reserpine, phenytoin and NaOH*

n	substances (mg/kg)	difference in α discharge $M \pm \sigma$	*p*	difference in γ discharge $M \pm \sigma$	*p*	α/γ quotient $M \pm \sigma$	—	$M \pm \sigma$	*p*
8	control — reserpine 10	*3.2* ± 1.2	<0.01	*—1.6* ± 1.8	0.05	*0.31* ± 0.11	—	*1.19* ± 0.45	< 0.01
	reserpine 10 — phenytoin 50	*—2.7* ± 2.0	<0.01	*2.1* ± 2.0	<0.02	*1.19* ± 0.45	—	*0.36* ± 0.20	< 0.01
8	control — reserpine 10	*3.5* ± 2.0	<0.01	*—3.1* ± 1.6	<0.01	*0.48* ± 0.20	—	*3.57* ± 2.25	< 0.01
	reserpine 10 — NaOH (pH 10)	*0.6* ± 0.9	—	*0.8* ± 1.2	—	*3.57* ± 2.25	—	*2,95* ± 1.97	—
8	control — phenytoin 50	*4.2* ± 2.7	<0.01	*1.6* ± 1.3	—	*0.61* ± 0.21	—	*0.96* ± 0.27	—
6	control — NaOH (pH 10)	*2.8* ± 2.8	<0.05	*2.2* ± 3.2	—	*0.79* ± 0.34	—	*0.95* ± 0.36	—

n number of experiments; *M* mean value; σ standard deviation.

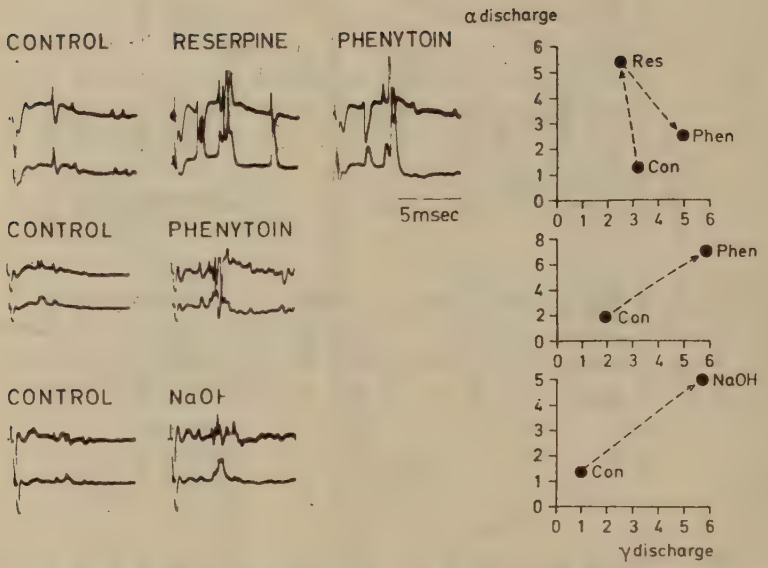

Fig. 6. Effect of reserpine, phenytoin and NaOH on motor control. The records represent α and γ reflex discharges from ventral root filaments (three different experiments). Note the increase of α and decrease of γ reflex discharge after reserpine, the increase of α and γ discharge after phenytoin (50 mg/kg) or NaOH when given alone, and the inhibition of the effect of reserpine by phenytoin. The diagram summarizes the experiments, giving the mean values of the number of α and γ discharges per sweep during the control period *Con*, after reserpine *Res*, phenytoin *Phen*, or *NaOH*

generally maximal at 30 to 40 min after the injection. Because of the basic reaction of the solution of phenytoin employed (pH 10), experiments with equal quantities (1.5 to 2.0 ml) of a solution of sodium hydroxide of the same alkalinity were performed, which showed no change of the state induced by reserpine (Table 7). It is unlikely, therefore, that the antagonizing effect of phenytoin is due to an alkalinization of the preparations. When phenytoin or a solution of sodium hydroxide were applied without pretreatment with reserpine, α reflex discharge was enhanced and, to some extent, also γ reflex discharge (Fig. 6; Table 7).

Discussion

All drugs tested in this study turned out to be effective against reserpine in "normalizing" the disturbed motor control. The results obtained with DOPA and atropine are in accordance with the findings of Steg and coworkers. Most of the drugs have already been shown to depress reserpine rigidity (Roos and Steg, 1964; Arvidsson *et al.*, 1966; Jurna, 1968 b), which may be attributed to an increased α motor activity.

Both cholinolytic and monoaminergic agents exerted a specific effect in reducing α and increasing γ reflex activity after pretreatment with reserpine, although, when given alone in high doses, they either left α and γ motor activity uninfluenced (atropine, biperiden, caramiphen, trihexyphenidyl, and DOPA), or even increased α activity (metamphetamine, propylhexedrine). Thus reserpine antagonism cannot be ascribed to a depressant action on the α motor system of the drugs *per se*. Since there is much evidence in favour of the view that motor disturbance produced by reserpine is due to an imbalance between monoaminergic and cholinergic functions in the brain, it might be assumed that reserpine antagonism results either from stimulation of monoaminergic mechanisms (DOPA, metamphetamine, propylhexedrine), or from reducing cholinergic activities (atropine, biperiden, caramiphen, trihexyphenidyl).

The quotient of α and γ reflex activity provides a useful index in evaluating the state of activity of both motor systems (ARVIDSSON *et al.*, 1966) and of the effect of drugs. However, a quotient of > 1, indicating predominance of α activity, does not require the existence of rigidity, because metamphetamine produces a similar increase of the quotient as reserpine (Table 2) without inducing rigidity. The similarity in the effect of reserpine and metamphetamine on α and γ reflex activity is paralleled by the finding that both substances lower electroseizure threshold when given separately (JURNA and REGÉLHY, 1968a). Lowering of the threshold was also observed after propylhexedrine, biperiden and atropine, but only biperiden increased the α/γ quotient to some extent (Table 5), whereas propylhexedrine stimulated both α and γ reflex discharge (Table 3). Thus no conclusions on the mode of action on electroseizure threshold of these drugs can be drawn from their effect on α and γ motor systems, especially when considering that an increase in α reflex activity is produced by phenytoin, which is an anticonvulsant agent. Its antireserpine action may result from inhibition of facilitatory processes following repetitive activation (ESPLIN, 1967; RAINES and STANDAERT, 1967).

Since predominance of α motor activity cannot be the sole reason for rigidity to develop, one has to look for a difference in the effects of reserpine on one hand and of metamphetamine or biperiden on the other. Such a difference exists in that the former shortens the latency of α reflex discharge, while the latter leave the interval between stimulus artifact and the first α reflex discharge unchanged. Normally, the α motoneurones tended to discharge with a rather long latency, the maxima of the intervals between stimulus artifact and the first α discharge being at 2.0 and 3.0 msec. After reserpine, the interval is reduced to about 1.5 msec, which corresponds fairly well to monosynaptic activation. Shortening of the latency is also obvious in Fig. 12 and 13 of the paper published by STEG in 1964. The action of reserpine on the latency of α

reflex discharge closely resembles the effect of a conditioning volley impinging on the motoneurones. The frequency of distribution of the intervals after reserpine show a tendency of synchronization of α reflex activity, which, in connection with increased α activity, may be an important factor in the development of rigidity.

Atropine given before the application of reserpine proved to be most effective in inhibiting motor disturbance. Out of the remaining number of cholinolytic agents, biperiden comes next in the effectiveness to "normalize" α and γ motor discharges as well as the latency of α discharge. Propylhexedrine was the most potent monoaminergic agent in restoring motor control and predominance of polysynaptic activity. Considering the latter criterium, the change in interval between stimulus artifact and the first α discharge, DOPA exhibited a much weaker effect.

The results obtained in this study provide further support of the view that disturbance of motor control caused by reserpine in the rat derives from an imbalance between monoaminergic and cholinergic systems in the brain, and suggest that rigidity, as a consequence of disturbed motor activity, may ensue from predominance and synchronization of α motor discharge.

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LEBENSLAUF:

Am 31. März 1945 wurde ich als Sohn des Zollhauptsekretärs Otto Lanzer und dessen Ehefrau Thekla geborene Matzenbacher in Kusel/Pfalz geboren. Nach dem Besuch der dortigen Volksschule wurde ich im April 1955 in das Staatliche Mathematisch-Naturwissenschaftliche Gymnasium Kusel aufgenommen, an dem ich am 13. Februar 1964 die Reifeprüfung ablegte.

Mein Medizinstudium nahm ich im Sommersemester 1964 an der Universität des Saarlandes auf. Nach bestandener naturwissenschaftlicher Vorprüfung im Mai 1965 und ärztlicher Vorprüfung im April 1967 legte ich auch dort am 13. Juli 1970 die ärztliche Prüfung ab.

Seit dem 1. September 1970 bin ich als Medizinalassistent in der Knappschaftsklinik Püttlingen tätig.